Exhibit R-2, RDT&E Budget Item Justification				Date: February 2005				
Appropriation/Budget Activity RDT&E,DW/BA2				R-1 Item Nomenclature: Medical Technology, PE 0602787D8Z				
Cost ($ in millions)	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008	FY 2009	FY 2010	FY 2011
Total PE Cost	11.588	13.204	0.000	0.000	0.000	0.000	0.000	0.000
Medical Technology/P505, Subtotal Cost	11.588	13.204	0.000	0.000	0.000	0.000	0.000	0.000

A. Mission Description and Budget Item Justification:

(U) This program supports applied research to investigate new approaches that will lead to advancements in biomedical strategies for preventing, treating, assessing and predicting the health effects of human exposure to ionizing radiation. Program objectives focus on mitigating the health consequences from exposures to ionizing radiation that represent the highest probable threat to US forces under current tactical, humanitarian and counter-terrorism mission environments. New protective and therapeutic strategies will broaden the military commander's options for operating within nuclear or radiological environments by minimizing both short- and long-term risks of adverse health consequences. Advancements in field-based biological dose assessment systems to measure radiation exposures will enhance triage, treatment decisions and risk assessment. Accurate models to predict casualties will promote effective command decisions and force-structure planning to ensure mission success.

(U) The program has three primary goals: (1) rational development of prophylactic and therapeutic strategies based on fundamental knowledge of radiation-induced pathophysiology and on leveraging advances in medicine and biotechnology from industry and academia; (2) development of novel biological markers and delivery platforms for rapid, field-based individual dose assessment; and (3) understanding toxic consequences from exposure to internal contamination from isotopes such as uranium.

B. Program Change Summary:

	FY 2004	FY 2005	FY 2006	FY2007
Previous President's Budget:	11.641	10.084	10.266	10.488
Current FY 2006 President's Budget Submission:	11.588	13.204	0.000	0.000
Adjustments to Appropriated Value:	-0.053	+3.120	-10.266	-10.488
Congressional Program Reductions:	-0.053	-0.280		
Congressional Rescissions:				
Congressional Increases:		+3.400		
Program Transfer:			-10. 266*	-10.488*
SBIR/STTR Transfers:				
Program Adjustment:				

*NOTE 1: Program transfers effective FY 2006 from RDT&E Budget Activity 3, Program Element 0602787D8Z to Defense Health Program (DHP).

NOTE 2: FY 2005 congressional increase of $3.4 for hibernation genomics to be transferred to appropriate agency for execution.

C. Other Program Funding Summary: Not applicable.

D. Acquisition Strategy: Not applicable.

E. Performance Metrics:
By FY 2006 identify at least 6 drugs or therapeutic approaches that are promising for treatment of radiation injury.
By FY 2008 identify at least 2 new biodosimetric approaches to determine individual radiation exposure.
By FY 2010 develop decision criteria for antibiotic use after radiation injury.

Exhibit R-2a, RDT&E Project Justification							Date: February 2005	
Appropriation/Budget Activity RDT&E, D BA 2				Project Name and Number Medical Technology, PE 0602787D8Z				
Cost ($ in millions)	FY 2004	FY 2005	FY 2006	FY 2007	FY 2008	FY 2009	FY 2010	FY 2011
Medical Technology/P505, Subtotal Cost	11.588	13.194	0.000	0.000	0.000	0.000	0.000	0.000

A. Mission Description and Budget Item Justification:

(U) This program supports applied research to investigate new approaches that will lead to advancements in biomedical strategies for preventing, treating, assessing and predicting the health effects of ionizing radiation.

(U) The program has three primary goals: (1) rational development of prophylactic and therapeutic strategies based on fundamental knowledge of radiation-induced pathophysiology and on leveraging advances in medicine and biotechnology from industry and academia; (2) development of novel biological markers and delivery platforms for rapid, field-based individual dose assessment; (3) understanding toxic consequences from chronic exposure to tissue-embedded depleted uranium (DU).

B. Accomplishments/Planned Program

Cost (in $ Millions)	FY 2004	FY 2005	FY 2006	FY 2007
Mechanisms of 5-AED Radioprotection	1.340	1.359	0.000	0.000

FY 2004 Accomplishments: To address the FDA requirement for an understanding of the mechanisms responsible for 5-AED's radioprotective actions, demonstrated that 5-AED modulates the spleen levels of several cytokines, which mediate signals of the immune system.

FY 2005 Plans: Initiate experiments on effects of 5-AED on the function of peritoneal macrophages, a critical, non-circulating component of the immune system. Continue to assess changes in cytokines in the spleen.

Cost (in $ Millions)	FY 2004	FY 2005	FY 2006	FY 2007
Radioprotective effects of isoflavones and vitamin derivatives	1.110	0.996	0.000	0.000

FY 2004 Accomplishments: Previously, demonstrated that the soybean derived isoflavone genistein has radioprotective effects. Improved the vehicle for administration of the isoflavones and determined the dose response curve for radioprotection by genistein in rodents. Determined the optimal time for administration of genistein for radioprotection. Completed the screening of tocopherol isomers - alpha, gamma, and delta-tocopherol for radioprotection; alpha and delta-tocopherols were found to be equally effective while gamma-tocopherol was less effective. Assessed the effects of alpha- tocopherol on radiation-induced thrombocytopenia (reduced the duration) and neutropenia (marginal improvement in recovery).

FY 2005 Plans: Establish the dose-response relationship for a second soy isoflavone, daidzein, for radiation protection and determine

the optimal time for administration. Evaluate the hematological effects of genistein with radiation exposure. Assess antimicrobial properties of genistein. Determine the dose-reduction factor of the most effective isomer of tocopherol. Compare pharmacokinetics of this isomer given subcutaneously in irradiated and non-irradiated mice.

Cost (in $ Millions)	FY 2004	FY 2005	FY 2006	FY 2007
Radioprotectants/Therapeutics Screening	2.110	1.998	0.000	0.000

FY 2004 Accomplishments: Continued systematic screening of potential radioprotectant and therapeutic compounds under a drug screen protocol. Among the drugs tested in FY2004 was a promising DHEA derivative that is effective in an oral preparation. Drugs that show potential will be targeted for further development. Evaluated drug release from liposomes using in vitro and in vivo (pharmacokinetic) assays.
FY 2005 Plans: Continued systematic survey of potential radioprotectant and therapeutic compounds under a drug screen protocol. There are currently about 20 drugs in the queue for analysis. Among those with the highest priority are CpG oligonucleotides, statins, SOD mimics, dipeptidyl peptidase inhibitors, and truncated flagellin.

Cost (in $ Millions)	FY 2004	FY 2005	FY 2006	FY 2007
PCC Cytogenetic Assay	0.230	0.515	0.000	0.000

FY 2004 Accomplishments: Optimized the temperature and humidity conditions for the premature chromosome condensation (PCC) aberration assay that permits rapid analysis of radiation exposure across a broad dose range from interphase lymphocytes of peripheral blood. Optimized the PCC induction protocol for small blood volumes.
FY 2005 Plans: Continue to improve sample preparation by promoting signal transduction mechanisms for inducing PCC in peripheral blood lymphocytes. These efforts will improve the efficiency of the assay.

Cost (in $ Millions)	FY 2004	FY 2005	FY 2006	FY 2007
Molecular Biomarkers- DNA mutations	0.456	0.534	0.000	0.000

FY 2004 Accomplishments: Developed real-time PCR for detection of DNA mutations (common mitochondria DNA deletion) in genomic DNA samples providing a significant advance in quantitative assessment of target sequences. Initiated studies to optimize the real-time and cytological DNA mutation bioassay to detect low-frequency DNA mutations.
FY 2005 Plans: Develop and evaluate modified deletion primers for quantitative fluid phase PCR bioassay in Human Peripheral Blood Lymphocytes (HPBL). Begin evaluation of low level multiplex detection.

Cost (in $ Millions)	FY 2004	FY 2005	FY 2006	FY 2007
Blood-Based Cell and Protein Markers	0.397	0.872	0.000	0.000

FY 2004 Accomplishments: Optimized the microassay to measure concentration of a specific marker protein (GADD45) in human blood samples. Characterized the relationship for GADD45 levels with radiation dose and post-exposure time, demonstrating feasibility of approach.
FY 2005 Plans: Initiate *in vitro* studies evaluating radiation-responsive blood protein biomarkers involving other protein targets. Initiate protein biomarker studies to evaluate inter-individual, partial body, and combined agent effects.

Cost (in $ Millions)	FY 2004	FY 2005	FY 2006	FY 2007
Toxicity of DU and Tungsten	0.433	0.020	0.000	0.000
FY 2004 Accomplishments: Determined that depleted uranium (DU) and tungsten alloys (WA) induce mutations in a marker gene (HPRT) in vitro; embedded WA causes rabdomyosarcoma in rats; DU can increase incidence of carcinogenicity in susceptible mice. (The related Defense Technology Objective completes in FY 2004.) FY 2005 Plans: Complete evaluation of heavy metals on viability of pulmonary macrophages and cell function.				
Cost (in $ Millions)	FY 2004	FY 2005	FY 2006	FY 2007
Late-Arising Radiation Injuries	0.205	0.401	0.000	0.000
FY 2004 Accomplishments: Determined that phenylacetate and epigallocatechin (EGCG) can effectively suppress radiation-induced human cell transformation in vitro (i.e, block development of pre-cancerous cells). FY 2005 Plans: Initiate radiation leukemogenesis studies with phenylacetate and EGCG.				
Cost (in $ Millions)	FY 2004	FY 2005	FY 2006	FY 2007
New Approaches to Treatment of Post Radiation Infection	1.969	1.603	0.000	0.000
FY 2004 Accomplishments: Identified the bacterial species that cause sepsis in lethally irradiated animal. Initiated in vitro studies on properties of probiotics (microbes that can be ingested to combat pathogenic bacteria of the gut). Determined that *Lactobacillus reuteri* is not susceptible to ciprofloxacin. FY 2005 Plans: Determine the effects of the quinolones against a polymicrobial infection from endogenous pathogens with lethal doses of radiation. Evaluate the effectiveness of *L. reuteri* as a probiotic protective agent when mice are challenged with *S. sonnei* and sub-lethal radiation exposure.				
Cost (in $ Millions)	FY 2004	FY 2005	FY 2006	FY 2007
Noninvasive “biomodulation” system (Congressional add)	2.400	0.000	0.000	0.000
FY 2004 Accomplishments: Funds were transferred to the appropriate agency for execution.				
Cost (in $ Millions)	FY 2004	FY 2005	FY 2006	FY 2007
Host-Defense Mechanisms	0.938	0.922	0.000	0.000
FY 2004 Accomplishments: Differentiated at least two mechanisms by which certain prospective radioprotectants protect mammalian cells from virally-induced cell death. FY 2005 Plans: Evaluate the effect of antioxidants and radioprotectants including genistein on changes induced by virus infection and radiation exposure using cell survival, apoptotic markers, and cytokine production as endpoints. Assess a variety of pathways that can result in cell death with and without viral infection in an effort to uncover cellular processes targeted by therapeutic drugs.				
Cost (in $ Millions)	FY 2004	FY 2005	FY 2006	FY 2007
Hibernation genomics (Congressional add)	0.000	3.400	0.000	0.000

NOTE: Funds to be transferred to appropriate agency for execution				
Cost (in $ Millions)	FY 2004	FY 2005	FY 2006	FY 2007
Internal contamination – Health Effects and countermeasures	0.000	0.574	0.000	0.000

FY 2005 Plans: Initiate studies to evaluate the effects of radioisotopes on a macrophage cell line in vitro to model the response of the lung macrophages to inhaled contaminants. To understand how late carcinogenic consequences develop after internal contamination and to develop effective countermeasures, studies will be initiated to evaluate the contribution of radiation (v. the chemical nature of the contaminant) to genomic instability and transformation.

C. Other Program Funding Summary: Not applicable.

D. Acquisition Strategy: Not applicable.

E. Major Performers: Armed Forces Radiobiology Research Institute, Bethesda, MD.